PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile: The Healthy Aging and Biomarkers Cohort Study (HABCS)
AUTHORS	Lv, Yue-Bin; Mao, Chen; Yin, Zhaoxue; Li, Fu-Rong; Wu, Xian-Bo; Shi, Xiaoming

VERSION 1 – REVIEW

REVIEWER	Angelo Scuteri Universita degli Studi di Sassari Italy
REVIEW RETURNED	27-Nov-2018

GENERAL COMMENTS	Authors provide an accurate and careful description of the study design, that likely can be shortened. The study population is large and adequate to test their hypothesis. However, Results are not clearly presented and with sufficient details. Evaluation of blood pressure in the context of the tested hypotheses is needed. Discussion should be written according to the presented Results with the appropriate and updated references.

REVIEWER	Martin Gulliford King's College London
REVIEW RETURNED	11-Dec-2018

GENERAL COMMENTS	This is a well-organised and well-written paper that describes the China Healthy Ageing and Biomarkers Cohort Study. The paper will be useful for researchers interested in epidemiological studies of ageing. 1. The paper is generally well-written but there are some minor typos: repaid=rapid, very=every etc 2. The paper points out that the HABCS study is a sub-study of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). There does not appear to be a comparable protocol paper for the CLHLS, which will be a useful counterpart to this paper. 3. It may be useful to add a Table showing basic descriptive data for the cohort in addition to the sample size data shown in Table 1. 4. Ethical issues and independent review may need mentioning.

	5. In the Results presented it will be reassuring to know that competing risks from morality were accounted for in reported associations, as mortality is quite high overall.

REVIEWER	Heidi TM Lai Friedman School of Nutrition Science and Policy, Tufts University, USA
REVIEW RETURNED	23-Jan-2019

GENERAL COMMENTS	The current report describes briefly about the cohort characteristics of The Healthy Aging and Biomarkers Cohort Study, including rationale for establishment and purpose, recruitment, follow-up, quality control, and data collection. The report also describes latest findings to date, including a brief description of associations between lipids and mortality and cognitive function, as well as vitamin D and cognitive function. Strengths and limitations are also addressed adequately. However, the report is submitted under the wrong category (Research) and should be re-submitted/changed to 'Cohort Profiles' instead. Subsequently, the report may be considered for acceptance after revisions according to the notes below: INTRODUCTION 1. In the sentence "…the oldest old is presenting a major challenge… because they often requires…", change to 'require' instead of requires. 2. Full study name needs to be reported before the abbreviation: HRS, SHARE, and LASI. COHORT DESCRIPTION Participants of HABCS 1. Given how this is a sub-cohort based on Chinese Longitudinal Healthy Longevity Survey, adequate references are needed to refer to shared methodology. 2. Please provide the % eligible in each province, % rejection rate, and the % who agreed to be interviewed per wave. 3. Please provide and reference and elaborate further on the use of a number mantissa over more common methods such as household/cluster sampling. 4. Please explain why it is important to have equal numbers of male/female participants. 5. For the sentences "As for gender matching… Otherwise, female participants will be selected instead.", please consider the use of a table/matrix to help readers interpret better. 6. Remove "in the very wave" from the sentence "We also try to re-interview those…". 7. Please report if participants were given any incentives to participate. Cohort follow-up and quality control 1. Further description is needed on how fieldwork is executed, for example, if there are designated times/days when teams would visit, which would affect the fasting state of blood samples and urine samples. Data collection 1. Reference needed for pilot studies mentioned in the text. 2. References needed for published methods, such as ADL and MMSE, and all other relevant methods listed in this section.

	3. Please report how deaths, chronic diseases, and hospitalizations were adjudicated. 4. Please indicate how fasting blood samples are collected, and state how many hours are participants required to fast for, e.g. 12-hours. 5. Please reword “Besides, 50ml urine sample is collected.” To “Additionally, 50 ml urine…”. 6. Please reword “…resulting in 9 tubes totally.” To “resulting in 9 tubes in total.”. 7. Please reword “Finally, the left urine sample…” to “Finally the remaining urine sample…”. 8. Please also indicate the type of urine sample collected, e.g. xx-hours, fasting/non-fasting. 9. Please indicate if how quickly (hours/days) the samples were processed from collection to storage, and at what temperature they were stored. 11. Please report how many times biological samples may be freeze-thawed, and if levels of biomarkers of interest are generally stable given multiple freeze-thaw cycles, with references. 12. Please also report methods to account for laboratory drift, and if other quality control methods were implemented. FINDINGS TO DATE Lipids and all-cause mortality 1. Please verify the sentence “This is the first study using a relatively large sample of oldest old to investigate the associations between LDL-C and all-cause mortality.” as there are older publications that have done so (see Jacobs 2013 at https://bmjopen.bmj.com/content/bmjopen/6/6/e010401.full.pdf). It may be more reasonable to say this is the first study to investigate this association in a non-Western population. 2. Given the short period of follow-up, please report if potential reverse causation was addressed. Vitamin D levels and cognitive function 1. Please briefly summarize the type of covariates that you have adjusted for. E.g. demographics, risk factors etc. 2. Given the short period of follow-up addressing baseline vitamin D levels and cognitive decline and impairment, please state briefly if potential reverse causation was addressed. STRENGTHS AND LIMITATIONS 1. For the statement “… through a resemble case-control design…”, please reword to “that resemble a case-control design”. Unless there is a good rationale for why the recruitment process is akin to case-control, I would suggest not to use this term as it may mislead readers. Please provide additional explanations in relevant sections. 2. Please elaborate on the term: “grass-roots health institutions”, as this is not a common term for readers based in the West. TABLE 1 1. Please provide % for each n. TABLE 2 1. Please elaborate IADL items as you’ve done for ADL.

REVIEWER	Theodora Katsila University of Patras, Greece

REVIEW RETURNED	04-Feb-2019

GENERAL COMMENTS	Overall, the authors have attempted a rather ambitious project, whose findings are of fundamental importance to various stakeholders, including health professionals, scientists, and policymakers. The rationale of the research strategy and study design are clear. Additionally to the current checklist, please see below for the major and minor concerns raised. Major comments: The authors present the limitations of their study. Yet, they need to clarify how and if they accounted for such confounding factors during their data analyses. Are (and if so, how) their findings expected to be affected? Same for deviations from the initial study design. In this study, eight longevity areas were selected by the Chinese Society of Gerontology. Is the population of these areas representative of the general population in China, apart from the fact of their high density of centenarians (considering that aging is clearly affected by environmental influences plus socio-economic factors)? Please also take into account the addition of the Rudong County later on (in 2012) as well as the HABCS data collection as reported in the manuscript. Are there any admixture effects (emphasis on genomics) anticipated regarding the population studied? Please clarify if samples were stored at -20C until their analysis and define this time-frame. Please state the time and speed for centrifugation and if this has been performed at room temperature or not. After the plasma vs blood separation, clarify how white blood cells were isolated and selected (as for someone to repeat the analysis per se). The authors claim that they focus on aging biomarkers, although they proceed with a targeted analysis of total cholesterol, LDL-C and vitamin D. The authors need to explain their decision making to explore such biomolecules, in particular as they are not aging specific biomarkers. Similar to above: were Table 3-indicators also included in data analysis? The authors need to elaborate on the statistical methods and information technologies used (plus statistical programme, version, etc), the parameters and variables in question and their overall reasoning. This is of paramount importance in terms of the claims made and the findings reported, especially when it comes to data validity and biases. Minor comments: l.9, p.6: please explain "very wave"

REVIEWER	Romana Novakovic Remedica Ltd Cyprus
REVIEW RETURNED	28-Feb-2019

GENERAL COMMENTS	Findings to date (Abstract section): needs some numbers, i.e. proportions with respect to findings that we see later on in the Results section. Rational (Introduction section) is concise and clear, i.e. how it builds up on existing data, and what the identified gaps are. The potential of the study is impressive (possibility to generate hypotheses for further studies or data analyses) - vast amount of data is and will be collected. For current manuscript, one would say that this is a methodology paper with preliminary data analyses. Methodology of sample analyses (blood, urine) did not change over time? It would be valuable to see regression coefficients for "The associations between all lipids and cognitive decline" in Lipid and cognitive function section, like it was nicely presented in Lipid and All-cause mortality section. I'm looking forward to see how covariates presented in Table 2 are related to biomarker concentrations. Some grammatical errors might be found, it needs further attention.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Angelo Scuteri
Institution and Country: Universita degli Studi di Sassari - Italy

1. Authors provide an accurate and careful description of the study design, that likely can be shortened.
Response: Thank you for this comment. We have shortened this section by removing some sentences, please refer to the revised manuscript.

2. The study population is large and adequate to test their hypothesis. However, Results are not clearly presented and with sufficient details.
Response: Thank you. The following details have been added to the results: covariates for adjustment, limitations and so on. Please refer to the revised manuscript.

3. Evaluation of blood pressure in the context of the tested hypotheses is needed.
Response: Thank you for your comment. The major objective of HABCS is to detect the association between biomarkers and several outcomes (e.g., cognitive function and mortality). To detect this association, we need to fully adjust for potential confounders such as body mass index, blood pressure. Traditionally, blood pressure is an important confounder for overall health. In this context, we need to evaluate blood pressure.

4. Discussion should be written according to the presented Results with the appropriate and updated references.
Response: Thank you. We have added updated references to this section. We have also introduced new publications in the Results section. Please refer to the revised manuscript for details.

Reviewer: 2
Reviewer Name: Martin Gulliford
Institution and Country: King's College London

1. The paper is generally well-written but there are some minor typos: repaid=rapid, very=every etc

Response: Thank you for your careful reading. We have tried our best to check the manuscript carefully and corrected similar errors as many as we can.

2. The paper points out that the HABCS study is a sub-study of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). There does not appear to be a comparable protocol paper for the CLHLS, which will be a useful counterpart to this paper.
Response: Thank you for your comment. So far, a comparable protocol paper (eg., a cohort profile for the CLHLS) is still not available. However, there are many publications reporting findings from CLHLS, among which the introduction of CLHLS could be found. In fact, we have also cited these publications in our manuscript. We hope these citations may help readers better understand the background of our research.

3. It may be useful to add a Table showing basic descriptive data for the cohort in addition to the sample size data shown in Table 1.
Response: Thank you for your suggestion, we have added a new table to the revised manuscript. Please refer to the revised manuscript for details.

4. Ethical issues and independent review may need mentioning.
Response: Thank you for this guidance. We have added this information accordingly. Please refer to the revised manuscript.

5. In the Results presented it will be reassuring to know that competing risks from morality were accounted for in reported associations, as mortality is quite high overall.
Response: Thank you for your comment. In the Results section, we presented the latest published findings from HABCS. Unfortunately, these findings were not accounted for competing risks. We have cited this as a limitation in the Results section.

Reviewer: 3
Reviewer Name: Heidi TM Lai
Institution and Country: Friedman School of Nutrition Science and Policy, Tufts University, USA

1. However, the report is submitted under the wrong category (Research) and should be re-submitted/changed to ‘Cohort Profiles’ instead. Subsequently, the report may be considered for acceptance after revisions according to the notes below:
Response: Thank you very much for your guidance. We have changed the category to “Cohort Profiles”.

INTRODUCTION
1. In the sentence “…the oldest old is presenting a major challenge… because they often requires…”, change to ‘require’ instead of requires.
Response: Thank you. We have revised the manuscript accordingly.

2. Full study name needs to be reported before the abbreviation: HRS, SHARE, and LASI.
Response: Thank you. We have revised the manuscript accordingly.

COHORT DESCRIPTION
Participants of HABCS
1. Given how this is a sub-cohort based on Chinese Longitudinal Healthy Longevity Survey, adequate references are needed to refer to shared methodology.
Response: Thank you for your comment. A few references were cited wherever necessary. Please refer to the revised manuscript.

2. Please provide the % eligible in each province, % rejection rate, and the % who agreed to be interviewed per wave.
Response: We apologize for failing to show this data. Unfortunately, this data have lost because the computer saving this data was damaged. We can only provide this information for the 2017 wave. We have added relevant information to the revised manuscript. Hope to get your understanding and support.

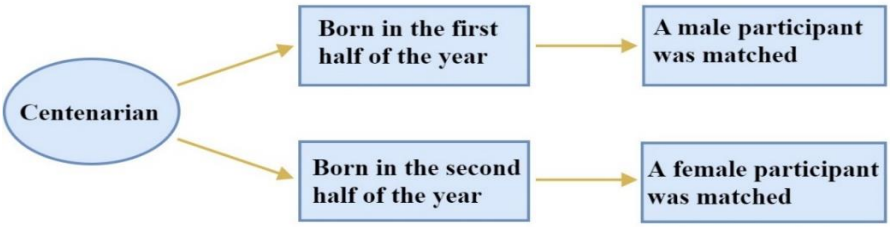
Table. The rejection rate and interview rate in 2017 wave survey.

District	Rejection rate (%)	Interview rate (%)
Rudong, Jiangsu	1.1	98.9
Laizhou, Shandong	0.3	99.7
Xiayi, Henan	10.4	89.6
ZHongxiang, Hubei	0.3	99.7
Mayang, Hunan	7.5	92.5
Dujiangyan, Sichuan	18.8	81.2
Yongfu, Guangxi	5.6	94.4
Chengmai, Hainan	10.9	89.1
Total	6.2	93.8

3. Please provide and reference and elaborate further on the use of a number mantissa over more common methods such as household/cluster sampling.
Response: Thank you for this comment. To avoid the problem of small sub-sample sizes at the more advanced ages, we did not follow the procedure of proportional sampling design, but instead interviewed nearly all centenarians and over-sampled the oldest old of more advanced ages. (Zeng Y, James VW., Xiao Z, et al. Chinese Longitudinal Healthy Longevity Survey (CLHLS), 1998-2005. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], 2009-06-04. https://doi.org/10.3886/ICPSR24901.v2)

4. Please explain why it is important to have equal numbers of male/female participants.
Response: Thank you for your comment. Detecting interaction has been a main concern in many cohort studies. We would like to detect whether findings are different between men and women in HABCS as gender is one of the most important effect modifier for interaction. However, we found that women had a larger proportion in comparison to men in the current study, this proportion seems to be larger among the oldest old. In fact, the unbalanced proportion would lead to the lack of statistical power needed to detect differences in subgroup analysis regarding women and men. Therefore, to get a relatively large number of men, we use a resemble case-control study by gender matching. We have added the following sentence to the revised manuscript as an explanation: “women had a larger proportion in comparison to men among the oldest old”.

5. For the sentences “As for gender matching… Otherwise, female participants will be selected instead.”, please consider the use of a table/matrix to help readers interpret better.
Response: Thank you for this comment. To help reader s interpret better, we have added a figure to the revised manuscript (shown as below). We hope this may help readers interpret better.



6. Remove “in the very wave” from the sentence “We also try to re-interview those…”.
Response: Thank you. We have revised the manuscript accordingly.

7. Please report if participants were given any incentives to participate.
Response: Thank you for your comment. All the interviewees are interviewed face-to-face at home, this process always takes at least an hour. Therefore, participants would receive incentives for delaying his/her work by the interview. Incentives are gifts that are worth no more than ¥30. We have added this information in the revised manuscript.

Cohort follow-up and quality control
1. Further description is needed on how fieldwork is executed, for example, if there are designated times/days when teams would visit, which would affect the fasting state of blood samples and urine samples.
Response: Thank for your comment. The sentence “Participants were informed in advance the designated times when the research teams would visit, and the blood was collected after an overnight fast.” was added to this section. Please refer to the revised manuscript.

Data collection
1. Reference needed for pilot studies mentioned in the text.
Response: Thank you for this comment. We have added a new reference to this section.

2. References needed for published methods, such as ADL and MMSE, and all other relevant methods listed in this section.
Response: Thank you for your guidance. We have added published methods regarding the above relevant methods to the revised manuscript accordingly.

3. Please report how deaths, chronic diseases, and hospitalizations were adjudicated.
Response: Thank you. We documented the date of death from the family members of the deceased or local doctors. Chronic diseases and hospitalizations were self-reported, as much as possible. We have added this information to the revised manuscript accordingly.

4. Please indicate how fasting blood samples are collected, and state how many hours are participants required to fast for, e.g. 12-hours.
Response: Blood samples were collected after an overnight fast (more than 12-hours). For all the interviewees, we collect 7ml venous blood sample (5ml+2ml) in total with two heparin anticoagulation blood collection tubes. Then the blood collection tubes were inverted 10 times immediately after the collection to mix the sample with the anticoagulant thoroughly. We have added this information to the revised manuscript.

5. Please reword “Besides, 50ml urine sample is collected.” To “Additionally, 50 ml urine…”.
Response: Thank you for this guidance. We have revised the manuscript accordingly.

6. Please reword “…resulting in 9 tubes totally.” To “resulting in 9 tubes in total.”.
Response: Thank you for this guidance. We have revised the manuscript accordingly.

7. Please reword “Finally, the left urine sample…” to “Finally the remaining urine sample…”.
Response: Thank you for this guidance. We have revised the manuscript accordingly.

8. Please also indicate the type of urine sample collected, e.g. xx-hours, fasting/non-fasting.
Response: Additionally, 50 ml urine sample is collected after an overnight fast (more than 12-hours). We have added this information to the revised manuscript.

9. Please indicate if how quickly (hours/days) the samples were processed from collection to storage, and at what temperature they were stored.
Response: Thank you for your good suggestion. Blood samples were centrifuged within one hour after blood collection for the separation of plasma from blood cell. Heparin anticoagulant blood samples were centrifuged at 3000 rpm for 10 minutes at 18-25 °C. Then all plasma, white blood cells, whole blood, and urine samples are stored at -80℃ in the county CDC. And then the sample were transported at -20℃with transport cases provided by CCDC by specially-assigned persons to designated testing units. After the plasma vs blood separation, natural sinking method was used to isolate white blood cells from red blood cells. We have added this information to the revised manuscript.

10. Please report how many times biological samples may be freeze-thawed, and if levels of biomarkers of interest are generally stable given multiple freeze-thaw cycles, with references.
Response: The freeze thaw only occurred once from the collection of biological samples to the determination of biomarkers. We have added this information to the revised manuscript.

12. Please also report methods to account for laboratory drift, and if other quality control methods were implemented.
Response: At the beginning of each shift, Laboratory quality control material was run. Levey–Jennings chart was plotted on to give a visual indication whether a laboratory test is working well. A mark is made indicating how far away the actual result was from the mean (which is the expected value for the control). Lines run across the graph at the mean, as well as one, two and three standard deviations to either side of the mean. This makes it easy to see how far off the result was. We have added this information to the revised manuscript.

FINDINGS TO DATE
Lipids and all-cause mortality
1. Please verify the sentence “This is the first study using a relatively large sample of oldest old to investigate the associations between LDL-C and all-cause mortality.” as there are older publications that have done so (see Jacobs 2013 at https://bmjopen.bmj.com/content/bmjopen/6/6/e010401.full.pdf). It may be more reasonable to say this is the first study to investigate this association in a non-Western population.
Response: Thank you very much for your careful reading. We have revised the manuscript accordingly.

2. Given the short period of follow-up, please report if potential reverse causation was addressed.
Response: Thank you for your comment. Only one of the cited study had tried to addressed potential reverse causation by conducting sensitivity analysis. To make this section clearer, we have cited this as a limitation wherever necessary. Please refer to the revised manuscript.

Vitamin D levels and cognitive function
1. Please briefly summarize the type of covariates that you have adjusted for. E.g. demographics, risk factors etc.
Response: Thank you. We have added the above information to this section.

2. Given the short period of follow-up addressing baseline vitamin D levels and cognitive decline and impairment, please state briefly if potential reverse causation was addressed.
Response: Thank you for your comment. Reverse causation was not addressed in this study. We have mentioned this as a limitation.

STRENGTHS AND LIMITATIONS
1. For the statement "… through a resemble case-control design…", please reword to "that resemble a case-control design". Unless there is a good rationale for why the recruitment process is akin to case-control, I would suggest not to use this term as it may mislead readers. Please provide additional explanations in relevant sections.
Response: Thank you for this kindly guidance. We have omitted this term throughout the revised manuscript.

2. Please elaborate on the term: "grass-roots health institutions", as this is not a common term for readers based in the West.
Response: Thank you. We have changed this term to "health care facilities"

TABLE 1
1. Please provide % for each n.
Response: Thank you for this comment. We have revised the table accordingly.

TABLE 2
1. Please elaborate IADL items as you've done for ADL.
Response: Thank you. We have elaborated IADL items accordingly.

Reviewer: 4
Reviewer Name: Theodora Katsila
Institution and Country: University of Patras, Greece

Major comments:
1. The authors present the limitations of their study. Yet, they need to clarify how and if they accounted for such confounding factors during their data analyses. Are (and if so, how) their findings expected to be affected? Same for deviations from the initial study design.
Response: Thank you for your valuable comment. So far, a few studies have reported some findings from HABCS. All these studies were reported in this cohort profile. Fortunately, all the publications in the Results section have tried to adjust for potential confounding factors using multivariate analysis. Moreover, sensitivity analysis also yielded relatively robust results. Therefore, we believe these results are reasonable. We also added some limitations to the Results section, so that readers could better interpret these results. Please refer to the revised manuscript. Thank you.

2. In this study, eight longevity areas were selected by the Chinese Society of Gerontology. Is the population of these areas representative of the general population in China, apart from the fact of their high density of centenarians (considering that aging is clearly affected by environmental influences plus socio-economic factors)? Please also take into account the addition of the Rudong County later on (in 2012) as well as the HABCS data collection as reported in the manuscript.
Response: Thank you for this professional comment. As HABCS was established to investigate the determinants of healthy aging, we thus selected longevity areas for sampling. However, compared with other areas, longevity areas have higher densities of centenarians and higher life expectancies. These areas (including Rudong County) may not be representative of the general population in China. The sentence "The areas (including Rudong County) we selected have higher densities of centenarians and higher life expectancies, this may partly due to the special environmental influences

plus socio-economic factors. Thus HABCS may not be representative of the general population in China." was added to the limitation section

3. Are there any admixture effects (emphasis on genomics) anticipated regarding the population studied?
Response: Thank you for this comment. The present study gathers comprehensive data for the elderly by simultaneously collecting, detecting, analyzing blood and urine, respectively. Unfortunately, we are not able to analyze admixture effects as we have not initiated DNA sequencing so far.

4. Please clarify if samples were stored at -20C until their analysis and define this time-frame. Please state the time and speed for centrifugation and if this has been performed at room temperature or not. After the plasma vs blood separation, clarify how white blood cells were isolated and selected (as for someone to repeat the analysis per se).
Response: Thank you for your good suggestion. Blood samples were centrifuged within one hour after blood collection for the separation of plasma from blood cell. Heparin anticoagulant blood samples were centrifuged at 3000 rpm for 10 minutes at 18-25 °C. Then all plasma, white blood cells, whole blood, and urine samples are stored at -80℃ in the county CDC. And then the sample were transported at -20℃with transport cases provided by CCDC by specially-assigned persons to designated testing units. After the plasma vs blood separation, natural sinking method was used to isolate white blood cells from red blood cells. We have added this information to the revised manuscript.

5. The authors claim that they focus on aging biomarkers, although they proceed with a targeted analysis of total cholesterol, LDL-C and vitamin D. The authors need to explain their decision making to explore such biomolecules, in particular as they are not aging specific biomarkers.
Response: Thank you for this comment. The major objective of HABCS is to detect the association between biomarkers and several outcomes (e.g., cognitive function and mortality). To detect this association, we need to fully adjust for potential confounders. In the present cohort profile, the biomarkers we focused on are either the confounding factors or the risk factors for adverse health outcomes in the older adults. The following explanation was added to the revised manuscript: "As HABCS was established to investigate the determinants of healthy aging. The biomarkers we focused on are either the confounding factors or the risk factors for adverse health outcomes in the older adults".

6. Similar to above: were Table 3-indicators also included in data analysis? The authors need to elaborate on the statistical methods and information technologies used (plus statistical programme, version, etc), the parameters and variables in question and their overall reasoning. This is of paramount importance in terms of the claims made and the findings reported, especially when it comes to data validity and biases.
Response: Thank you for this thoughtful comment. HABCS is a cohort profile, we concluded results from publications that focused on data of HABCS. These studies mainly reported associations between biomarker concentrations and several outcomes (e.g., cognitive function and mortality). As a result, statistical methods and information technologies vary substantially across different studies. Therefore, it is very difficult and my not be needed to elaborate on all the details of the publications we cited. Hope for your kindly understanding.

Minor comments:
l.9, p.6: please explain "very wave"
Response: We apologize for this confusion. It should be "every". we have corrected this error.

Reviewer: 5
Reviewer Name: Romana Novakovic
Institution and Country: Remedica Ltd - Cyprus
1. Findings to date (Abstract section): needs some numbers, i.e. proportions with respect to findings that we see later on in the Results section.
Response: Thank you for this suggestion. We have added some numbers accordingly. Please refer to the revised manuscript.

2. Rational (Introduction section) is concise and clear, i.e. how it builds up on existing data, and what the identified gaps are. The potential of the study is impressive (possibility to generate hypotheses for further studies or data analyses) - vast amount of data is and will be collected. For current manuscript, one would say that this is a methodology paper with preliminary data analyses.
Response: We apologize for this confusion. The present study is a cohort study. We aimed to introduce the study design, study population and more importantly, the results from those publications which reported findings based on the data from HABCS. To avoid misunderstanding, we have changed the title to “Cohort Profile: The Healthy Aging and Biomarkers Cohort Study (HABCS)”.

3. Methodology of sample analyses (blood, urine) did not change over time?
Response: Thank you for this comment. According to our project, all laboratory analyses are conducted by the central clinical lab at Capital Medical University in Beijing, and the Methodology of sample analyses will not change over time.

4. It would be valuable to see regression coefficients for “The associations between all lipids and cognitive decline” in Lipid and cognitive function section, like it was nicely presented in Lipid and All-cause mortality section.
Response: Thank you for this guidance. We have added regression coefficients to this section.

5. I’m looking forward to see how covariates presented in Table 2 are related to biomarker concentrations.
Response: We apologize for this confusion. The present study is a cohort profile. So far, a few studies regarding associations between various biomarker concentrations and outcomes (cognitive function or mortality) have been published. However, the covariates presented in Table 2 have not yet been fully explored. As the data of HABCS are publicly available, we believe that more and more studies will be available in the future.

6. Some grammatical errors might be found, it needs further attention.
Response: Thank you. We have tried our best to check the manuscript carefully and corrected similar errors as many as we can.

VERSION 2 – REVIEW

REVIEWER	Theodora Katsila National Hellenic Research Foundation, Greece
REVIEW RETURNED	02-Apr-2019

GENERAL COMMENTS	The authors did their very best and addressed all my comments

REVIEWER	Romana Novakovic Remedica Ltd, Cyprus
REVIEW RETURNED	21-Apr-2019

GENERAL COMMENTS	The publication is now significantly improved.